Cochrane Library

Cochrane Database of Systematic Reviews

Saline irrigation for the management of skin extravasation injury in neonates (Review)

Gopalakrishnan PN, Goel N, Banerjee S

Gopalakrishnan PN, Goel N, Banerjee S.
Saline irrigation for the management of skin extravasation injury in neonates.
Cochrane Database of Systematic Reviews 2017, Issue 7. Art. No.: CD008404.
DOI: 10.1002/14651858.CD008404.pub3.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Review]

Saline irrigation for the management of skin extravasation injury in neonates

P N Gopalakrishnan[1], Nitin Goel[2], Sujoy Banerjee[2]

[1]Department of Neonatology, Wishaw General Hospital, Wishaw, UK. [2]Department of Neonatology, Singleton Hospital, ABM University Health Board, Swansea, UK

Contact address: P N Gopalakrishnan, Department of Neonatology, Wishaw General Hospital, 50 Netherton St, Wishaw, Lanarkshire, Scotland, ML2 0DP, UK. sukagopa@hotmail.com.

Editorial group: Cochrane Neonatal Group.
Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 7, 2017.

Citation: Gopalakrishnan PN, Goel N, Banerjee S. Saline irrigation for the management of skin extravasation injury in neonates. *Cochrane Database of Systematic Reviews* 2017, Issue 7. Art. No.: CD008404. DOI: 10.1002/14651858.CD008404.pub3.

ABSTRACT

Background

Extravasation injury, a complication commonly seen in the neonatal intensive care unit, can result in scarring with cosmetic and functional sequelae. A wide variety of treatments are available, including subcutaneous irrigation with saline (with or without hyaluronidase), liposuction, use of specific antidotes, topical applications, and normal wound care with dry or wet dressings. All such treatments aim to prevent or reduce the severity of complications.

Objectives

Primary objective

To compare the efficacy and safety of saline irrigation or saline irrigation with prior hyaluronidase infiltration versus no intervention or normal wound care for tissue healing in neonates with extravasation injury.

Secondary objectives

To evaluate by subgroup analysis of controlled trials the influence of type of extravasate, timing of irrigation following extravasation, and postmenstrual age (PMA) of the neonate at the time of injury on outcomes and adverse effects.

Specifically, we planned to perform subgroup analysis for the primary outcome, if appropriate, by examining:

1. time to irrigation from identified extravasation injury (< 1 hour or ≥ 1 hour);

2. type of extravasate (parenteral nutrition fluid or other fluids or medications);

3. amount of saline used (< 500 mL or ≥ 500 mL); and

4. PMA at injury (< 37 completed weeks or ≥ 37 completed weeks).

Search methods

We used the standard search strategy of the Cochrane Neonatal Review Group to search the Cochrane Central Register of Controlled Trials (CENTRAL; 2017, Issue 1), MEDLINE via PubMed (1966 to 2 February 2017), Embase (1980 to 2 February 2017), and the Cumulative Index to Nursing and Allied Health Literature (CINAHL; 1982 to 2 February 2017). We also searched clinical trial databases, conference proceedings, and reference lists of retrieved articles for randomised controlled trials and quasi-randomised trials. We used the Google Scholar search tool for reverse citations of relevant articles.

Selection criteria

Randomised controlled trials (RCTs) and quasi-randomised controlled trials comparing saline irrigation with or without hyaluronidase infiltration versus no intervention or normal wound care for the management of extravasation injury in neonates.

Data collection and analysis

Three review authors independently reviewed and identified articles for possible inclusion in this review. We used the GRADE approach to assess the quality of evidence.

Main results

We found no eligible studies. Our search revealed 10 case reports or case series describing successful outcomes with different interventions for this condition.

Authors' conclusions

To date, no RCTs have examined the effects of saline irrigation with or without prior hyaluronidase infiltration for management of extravasation injury in neonates. Saline irrigation is frequently reported in the literature as an intervention for management of extravasation injury in neonates. Research should focus first on evaluating the efficacy and safety of this intervention through RCTs. It will also be important for investigators to determine effect size by examining the timing of the intervention, the nature of the infusate, and severity of injury at the time of intervention.

PLAIN LANGUAGE SUMMARY

Saline irrigation for the management of skin extravasation injury in neonates

Review question: How does saline irrigation or saline irrigation with prior hyaluronidase compare with no intervention or normal wound care for improving tissue healing in neonates with extravasation injury?

Background: Preterm and sick term infants requiring intravenous fluids and medications are vulnerable to tissue injury secondary to extravasation, that is, leakage of fluid into surrounding tissue. Such injury can result in scarring with consequent cosmetic issues and, in some infants, functional limitations. Remedial surgical intervention may be required for some babies. Saline flush, with or without prior infiltration of hyaluronidase (a protein that promotes the breakdown of barriers that hold tissue planes together), is widely used for the management of severe extravasation injury in neonates, and is intended to prevent or reduce complications following extravasation. Conservative treatment with normal wound care and various topical dressings is commonly used at different stages of extravasation injury with variable results.

Study characteristics: We found no high-quality randomised or quasi-randomised studies that currently answer this question.

Key results: To date, no randomised controlled trials have examined the effects of saline irrigation with or without prior hyaluronidase infiltration on the management of extravasation injury in neonates. Frequent reports in the literature indicate that saline irrigation is used for the management of extravasation injury in neonates. Research should be directed first toward evaluating the efficacy and safety of this intervention through randomised controlled trials. It will also be important to determine effect size by examining the timing of the intervention, the nature of the infusate, and severity of injury at the time of intervention.

Quality of evidence: We obtained very low-quality evidence from case series or reports.

Summary of findings for the main comparison. Saline irrigation with or without prior infiltration of hyaluronidase vs standard wound care for management of extravasation injury in neonates

Saline irrigation with or without prior infiltration of hyaluronidase vs standard wound care for management of extravasation injury in neonates

Patient or population: neonates requiring management of extravasation injury
Setting: neonatal intensive care units
Intervention: saline irrigation with or without prior infiltration of hyaluronidase
Comparison: standard wound care

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with standard wound care	Risk with saline irrigation with or without prior infiltration of hyaluronidase				
Complete wound healing after saline irrigation with or without prior hyaluronidase infiltration (wound healing): clinical assessment	Study population		Not estimable	237 (10 observational studies)	⊕⊖⊖⊖ Very low	Pooled data for 237 neonates from 10 case report studies who underwent saline irrigation. Three neonates received further surgical intervention. For 234 neonates, complete wound healing was reported
	0 per 1000	0 per 1000 (0 to 0)				

*__The risk in the intervention group__ (and its 95% confidence interval) is based on assumed risk in the comparison group and __relative effect__ of the intervention (and its 95% CI)

CI: confidence interval; OR: odds ratio; RR: risk ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to the estimate of effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of effect but may be substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

All 10 studies analysed in GRADE pro GDT are case reports, and the intervention methods mentioned are highly variable. In view of this, "relative effect (95% CI)" and "absolute effect (95% CI)" were not derived.

BACKGROUND

Description of the condition

Many preterm and sick term infants in neonatal intensive care units (NICUs) require intravenous nutrition and medication as part of their care and are particularly vulnerable to extravasation (leakage of fluid into surrounding tissue) injury. Extravasation or infiltration of intravenous fluid into surrounding tissue is known to occur at some point in up to 70% of neonates undergoing intensive care (Irving 1999). A survey of regional NICUs in the United Kingdom (UK) reported the prevalence of extravasation injury resulting in skin necrosis (local tissue death) as 38/1000 neonates, with 70% of these injuries occurring in infants at 26 weeks' gestation or less (Wilkins 2004). About 4% of infants leave the NICU with cosmetically or functionally significant scars caused by extravasation injury (Wilkins 2004). Extravasation of intravenous infusion into the interstitial space may result from displacement of the intravascular catheter or increased vascular permeability. Some medications and infusions are more toxic to the veins than others. The mechanism of extravasation necrosis is not completely understood, but the degree of damage appears to be related to osmolality, pH, and dissociability of ions within the infusate (intravenous fluid) (Davies 1994; Goutos 2014).

Depending on the nature and volume of the infusate, extravasation may go unnoticed or may cause severe inflammation. In the short term, this may lead to partial or complete skin loss, infection, nerve or tendon damage, and, infrequently, compartment syndrome leading to amputation of the affected limb (Gault 1993). Scarring leading to contractures and disfigurement, functional loss of the affected part, complex regional pain syndrome (Hadaway 2007), and major limb deformities (Fullilove 1997) are well known long-term sequelae (Cartlidge 1990). It has been reported that 70% of scars sustained by minor extravasation injury disappeared by eight years of age, and that more serious but less prominent scars were still seen at eight years of age (Fox 1998).

Researchers have classified extravasation injury into four stages (Millam 1988; Flemmer 1993; McCullen 2006).

1. Stage 1: painful intravenous site, no erythema and swelling, flushes with difficulty.
2. Stage 2: painful intravenous site, slight swelling, redness, no blanching, brisk capillary refill below infiltration site, good pulse volume below infiltration site.
3. Stage 3: painful intravenous site, marked swelling, blanching, cool to touch, brisk capillary refill below infiltration site, good pulse volume below infiltration site.
4. Stage 4: painful intravenous site, very marked swelling, blanching, cool to touch, capillary refill longer than four seconds, decreased or absent pulse, skin breakdown or necrosis.

The best management approach is preventative and requires hypervigilant monitoring of the intravenous site (Patnaik 2004). However, once extravasation has occurred, the best practice for reducing tissue damage and its consequent complications is a topic of controversy. Available treatments include irrigation with saline (with or without prior infiltration of hyaluronidase), liposuction, use of specific antidotes, various topical applications, and normal wound management with dry or wet dressings (Ramasethu 2004). Successful outcomes without sequelae have been reported with multiple needle puncture of the extravasation site, followed by gentle squeezing (Chandanvasu 1986). Various topical applications such as silver sulphadiazine cream (Friedman 1998); silver sulphadiazine ointment, topical povidone-iodine ointment, and saline wash (Brown 1979); topical application of silver sulphadiazine and paraffin tulle (Kumar 2001); hydrocolloid gel (Thomas 1997; Sawatzky-Dickson 2006); fibrinolysin and deoxyribonuclease ointment (Falcone 1989); and a combination of antibacterial ointment, sesame oil, and an herbal mixture (Cho 2007) have all been reported to be effective. In a tense extravasation injury, gentle massaging of the affected limb to allow good capillary flush has been found to be beneficial (Davidson 1985). Infiltration of 'recombinant human hyaluronidase' (rHuPH20) into the extravasation injury site has been reported (Kuensting 2010). Topical application of maternal platelet-rich plasma (PRP) has been shown to produce encouraging results for a necrotic extravasation wound (Lee 2013). Use of topical hyalomatrix PA over the eschar wound that developed after extravasation injury and was treated with saline irrigation resulted in restoration of re-epithelialisation and dermal neoformation (Onesti 2012). It has been suggested that the effectiveness of the intervention may depend on the injury-intervention interval (Casanova 2001), or the necrosis interval (Goutos 2014). Limb elevation has proved effective when extravasation resulted in erythema and swelling (Reynolds 2007). The stage of injury at the time of intervention may be important, and it has been suggested that saline irrigation for stage 3 or 4 extravasation may prevent further damage (Sawatzky-Dickson 2006; Kostogloudis 2015). Non-pharmacological intervention measures have been described in a recently published paper (Reynolds 2014).

Description of the intervention

Subcutaneous irrigation for extravasation injury is carried out by the 'flush-out technique', which was first proposed by David Gault in 1993 (Gault 1993). Dilute hyaluronidase is infiltrated into the affected area following local anaesthetic infiltration under aseptic conditions. Four small stab incisions are made around the periphery of the extravasated area. Saline is then infiltrated into the subcutaneous tissue in small volumes of 20 to 50 mL (Gault 1993) with a blunt-ended needle with a side hole, so it dilutes the extravasate and comes out freely through exit stab incisions. A total of 500 mL of saline is recommended for the 'flush-out' (Gault 1993; Davies 1994; Harris 2001). Residual fluid is then manipulated down to the exit holes and is expressed. After flush-out, a wound dressing is applied, and the limb is elevated for 24 hours.

Although this is the standard procedure described by Gault, investigators have noted wide variation in the flush-out process, the dosage of hyaluronidase infiltrated (Bruera 1999), and the total volume of saline used for irrigation. The published literature does not provide specific guidance on the time interval allowed between injection of hyaluronidase and subsequent saline flush-out. However, most reports mention that flush-out should be undertaken soon after hyaluronidase infiltration.

How the intervention might work

Immediate saline irrigation with or without hyaluronidase is used increasingly in neonatal units across the world. The idea is that saline irrigation will dilute the extravasate and flush it out from

the local area as quickly as possible. This technique is theoretically possible in neonates, who have very little subcutaneous fat.

Hyaluronidase is an enzyme that hydrolyses the mucopolysaccharides present in subcutaneous connective tissue. Hyaluronidase reversibly hydrolyses hyaluronic acid polymers within the extracellular space (Jaworski 1950). This is thought to enhance permeability within the subcutaneous tissue compartment while allowing diffusion of the extravasate through larger areas in the subcutaneous space, which then can be flushed out more easily by saline irrigation (PPAG 2005).

Why it is important to do this review

Extravasation injury is associated with serious morbidity in neonates. In the short term, this injury may cause pain, tissue necrosis, ulceration, and infection. Extravasation may prevent infusion of needed medications, which in itself can cause dire consequences. In the medium to long term, this may lead to scar formation with disfigurement and functional impairment. If effective, saline irrigation with or without hyaluronidase infiltration may reduce this morbidity. However, the intervention is highly invasive and involves a great deal of manual handling of the sick and vulnerable neonate. It can lead to pain, hypothermia, infection, and cardiorespiratory destabilisation. The multiple stab incisions integral to the procedure may result in scar formation. It is important to establish if, for the short and long term, this form of intervention is superior to conservative wound management.

OBJECTIVES

Primary objective

To compare the efficacy and safety of saline irrigation or saline irrigation with prior hyaluronidase infiltration versus no intervention or normal wound care for tissue healing in neonates with extravasation injury.

Secondary objective

To evaluate by subgroup analysis of controlled trials the influence of type of extravasate, timing of irrigation following extravasation, and postmenstrual age (PMA) of the neonate at the time of injury on outcomes and adverse effects.

Specifically, we planned to perform subgroup analysis for the primary outcome, if appropriate, by examining:

1. time to irrigation from identified extravasation injury (< 1 hour or ≥ 1 hour);
2. type of extravasate (parenteral nutrition fluid or other fluids or medications);
3. amount of saline used (< 500 mL or ≥ 500 mL); and
4. PMA at injury (< 37 completed weeks or ≥ 37 completed weeks).

METHODS

Criteria for considering studies for this review

Types of studies

All randomised and quasi-randomised controlled trials comparing saline irrigation, with or without hyaluronidase infiltration, versus no intervention or normal wound care only. We considered as eligible relevant studies published only as abstracts in conference proceedings, and we contacted principal trial authors for further details. We applied no language restrictions.

Types of participants

Neonates of any gestational age at birth (defined as up to 28 days of postnatal age at enrolment) with extravasation of intravenous infusate from peripheral or central venous catheters, when extravasation has led to any one of the following.

1. Moderate swelling and erythema of the overlying area.
2. Blanching or discolouration of the overlying skin.
3. Pressure symptoms (capillary refill longer than four seconds and reduced or absent pulse below the site of extravasation).
4. Ulceration of the overlying skin.

Types of interventions

Irrigation therapy is defined as any intervention by which saline is instilled into the site of extravasation, with the aim of diluting the extravasate, followed by provision for it to drain through the skin incisions. Any prior infiltration with hyaluronidase and its dosage are also recorded.

Normal wound care is defined as care involving no irrigation or other invasive interventions but including wound care with dry or wet dressings and wound debridement if clinically indicated.

Types of outcome measures

Primary outcomes

Complete tissue healing (defined as no residual breach of skin or inflammatory signs) without scar formation at discharge or latest assessment, preferably at least three months from the time of injury, as complete wound healing is expected by this time.

Secondary outcomes

Short-term outcomes

1. Time to complete tissue healing.
2. Infection, defined as at least one of the following.
   a. Purulent discharge from the site.
   b. Organisms isolated from an aseptically obtained culture of fluid or tissue derived from the site.
   c. Clinical diagnosis made by the physician requiring topical or systemic antibiotics.
3. Pain during the intervention (measured on validated neonatal pain scales).
4. Hypothermia during or at the end of the intervention (defined as temperature < 36°C or a drop of 2°C from baseline measurement).
5. Anaphylactic reactions.
6. Fluid and electrolyte status.
7. Any other adverse effects reported by trial investigators.

Long-term outcomes

These include the following outcomes as measured in the latest assessment, preferably at least three months after injury.

1. Severity of the scar, as measured by a quantifiable validated scar scale. Scar measurement scales could include, but are not limited to, the Vancouver Scar Scale, a visual analogue

scale, the Patient and Observer Scar Assessment Scale, and the Manchester Scale.

2. Contracture – permanent tightening of non-bony tissues such as muscles, tendons, ligaments, or skin, with or without restriction of joint motion (dichotomous outcome).
3. Functional impairment – restriction of function of the injured body part, as reported by caregivers or by the physician (dichotomous outcome).
4. Disfigurement - substantial scarring that is cosmetically offensive, as measured by caregivers or by the reporting physician (dichotomous outcome).
5. Need for additional surgical procedures.

Search methods for identification of studies

We used the criteria and standard methods of the Cochrane Collaboration and the Cochrane Neonatal Review Group (see the Cochrane Neonatal search strategy for the specialised register).

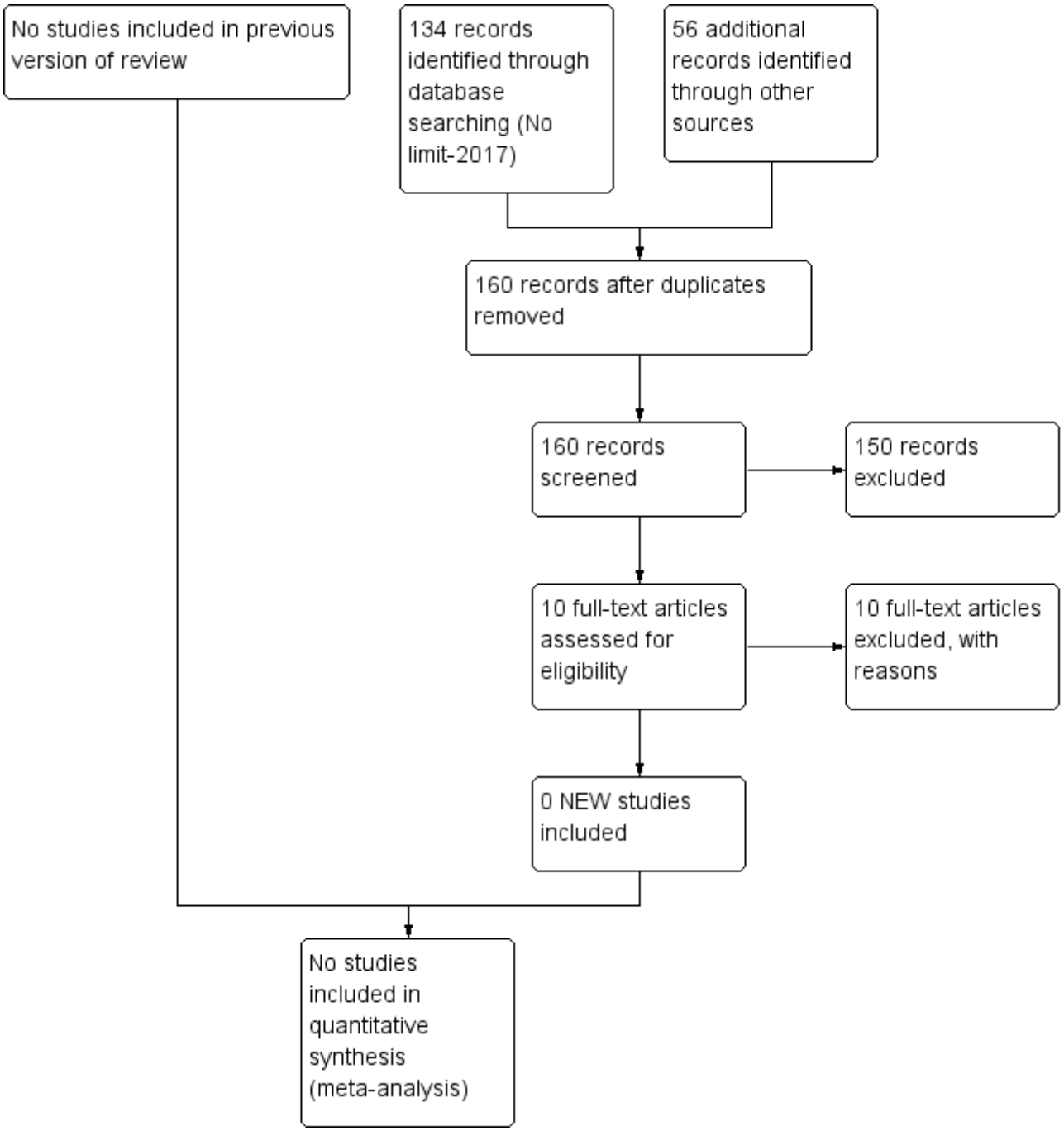
Electronic searches

We conducted a comprehensive search of the following databases: Cochrane Central Register of Controlled Trials (CENTRAL; 2017, Issue 1) in the Cochrane Library; MEDLINE via PubMed (1966 to 2 February 2017); Embase (1980 to 2 February 2017); and the Cumulative Index to Nursing and Allied Health Literature (CINAHL; 1982 to 2 February 2017). We used the following search terms: (extravasation OR ((inflammation OR swelling OR edema OR erythema) AND catheter* OR intravenous fluid*)) AND (saline OR hyaluronidase OR hyaluronoglucosaminidase OR irrigation), plus database-specific limiters for RCTs and neonates (see Appendix 1 for the full search strategy for each database). We removed language restrictions during the search update for this review.

We searched clinical trial registries for ongoing and recently completed trials (clinicaltrials.gov; the World Health Organization International Clinical Trials Registry and Platform - www.whoint/ictrp/search/en/; and the ISRCTN Registry - www.isrctn.com).

Ms Jennifer Spano from the Cochrane Neonatal Review Group performed a parallel search; Figure 1 presents the search flow diagram.

Figure 1. Study flow diagram: review update.



We performed a 'reverse citation' search of relevant articles using Google Scholar.

See Appendix 2 for searches run for the previously published review.

Searching other resources

We reviewed reference lists from the above articles and from review articles on the topic. When relevant, we attempted to communicate with primary authors of the studies above to identify unpublished data.

We searched the following.

1. Proceedings of the Nutrition Society: Nestle Foundation (2004).
2. Proceedings of summer meetings of the British Association of Plastic Surgeons (2001 to 2010).
3. Proceedings of annual conferences of the European Society for Paediatric Research (2001 to 2010).
4. Proceedings of the Pediatric Academic Societies (2001 to 2010).

We retrieved one abstract from the abstract archives of the Pediatric Academic Societies meetings and found that it was not relevant to this review (Valente 2001).

We could not retrieve in full one abstract from the Proceedings of the British Association of Plastic Surgeons Summer Meeting held in July 2001. Therefore, we contacted the primary author of the presentation (Moss 2001) by email. The primary author replied to inform us that currently he has no access to the abstract.

Data collection and analysis

We used standardised methods of the Cochrane Collaboration and the Cochrane Neonatal Review Group.

Selection of studies

Three review authors independently reviewed all identified articles for possible inclusion in this review. In the event of disagreement on the suitability of a trial for inclusion, we reached consensus by discussion.

Data extraction and management

Each review author extracted data separately using pre-designed data extraction forms; we then compared results. However, we identified no suitable randomised controlled trial (RCT) or quasi-RCT for further analysis.

Assessment of risk of bias in included studies

Two review authors (NG, SB) independently assessed the risk of bias (low, high, or unclear) of all included trials using the Cochrane 'Risk of bias' tool (Higgins 2011) for the following domains.

1. Sequence generation (selection bias).
2. Allocation concealment (selection bias).
3. Blinding of participants and personnel (performance bias).
4. Blinding of outcome assessment (detection bias).
5. Incomplete outcome data (attrition bias).
6. Selective reporting (reporting bias).
7. Any other bias.

We resolved disagreements by discussion or by consultation with a third assessor. See Appendix 3 for a detailed description of risk of bias for each domain.

Measures of treatment effect

We planned to use standardised statistical methods of the Cochrane Collaboration. For categorical data, we aimed to calculate risk ratio (RR), risk difference (RD), number needed to treat for an additional beneficial outcome (NNTB), and number needed to treat for an additional harmful outcome (NNTH). For continuous data, we aimed to calculate weighted mean difference (WMD). We planned to report the 95% confidence interval (CI) for all estimates.

Unit of analysis issues

We planned to analyse results reported for individual infants.

Dealing with missing data

We planned to contact principal authors when data were missing; as the search for this review yielded only case reports or series, we did not need to do so.

Assessment of heterogeneity

We planned to undertake an assessment of heterogeneity, if applicable, by using the I^2 statistic, and to consider 25% as low and 75% as high heterogeneity.

Assessment of reporting biases

This assessment was not applicable.

Data synthesis

Quality of evidence

We used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach, as outlined in the *GRADE Handbook* (Schünemann 2013), to assess the quality of evidence for the following (clinically relevant) outcomes: complete wound healing with no functional and cosmetic complications.

Two review authors (PG, NG) independently assessed the quality of evidence for each of the outcomes above. We planned to consider evidence from RCTs as high quality but to downgrade the evidence by one level for serious (or two levels for very serious) limitations on the basis of the following: design (risk of bias), consistency across studies, directness of evidence, precision of estimates, and presence of publication bias. We used the GRADEpro GDT Guideline Development Tool to create a 'Summary of findings' table to report the quality of the evidence.

The GRADE approach yields an assessment of the quality of a body of evidence according to one of four grades.

1. High. We are very confident that the true effect lies close to the estimate of effect.
2. Moderate. We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of effect but may be substantially different.
3. Low. Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of effect.
4. Very low. We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Subgroup analysis and investigation of heterogeneity

We planned to perform subgroup analysis, if appropriate, for the primary outcome by examining:

1. time to irrigation from identified extravasation injury (< 1 hour or ≥ 1 hour);
2. type of extravasate (parenteral nutrition fluid or other fluids OR medications);
3. amount of saline used (< 500 mL or ≥ 500 mL); and
4. corrected gestation at injury (< 37 completed weeks or ≥ 37 completed weeks).

However, we did not undertake this analysis, as we identified no suitable data for analysis.

Sensitivity analysis

This was not applicable.

RESULTS

Description of studies

By applying the search strategy, we identified no RCTs or quasi-RCTs for this review, but we found several case reports, case series, and cohort studies. As we retrieved no RCTs or quasi-RCTs for the intended study age group, we repeated the search with no age restrictions and still did not identify any relevant studies that matched our inclusion criteria.

Results of the search

We identified one relevant case report published since the original review was presented in 2012 (Kostogloudis 2015).

Included studies

We found no eligible RCTs or quasi-RCTs and included no studies in this review.

Excluded studies

Ten studies identified by the search were not eligible for inclusion but have been used for discussion and are mentioned below under additional tables (Gault 1993; Davies 1994; Martin 1994; Chen Y Y 1996; Casanova 2001; Harris 2001; Chowdhury 2004; Siu 2007; Kuensting 2010; Kostogloudis 2015 (Table 1; Table 2; Characteristics of excluded studies).

Risk of bias in included studies

This was not applicable, as we found no eligible studies.

Allocation

This was not applicable, as no randomised controlled trials are available.

Blinding

This was not applicable.

Incomplete outcome data

This was not applicable, as the search for this review identified only case reports.

Selective reporting

This was not applicable.

Other potential sources of bias

This was not applicable.

Effects of interventions

See: **Summary of findings for the main comparison** Saline irrigation with or without prior infiltration of hyaluronidase vs standard wound care for management of extravasation injury in neonates

No results are forthcoming, as we identified no eligible studies.

DISCUSSION

Although our search identified no relevant trials for this review, we present a brief summary of case reports and case series on this topic that highlight important issues related to current practice and practice variations when saline irrigation with or without hyaluronidase infiltration is the main intervention. Most reports describe good outcomes, but this may reflect the publication bias that is inherent in case reports.

In a retrospective review of all venous line-related extravasation injuries among neonates in the neonatal intensive care unit (NICU) and in the surgical ward over an 18-month period, healthcare providers treated 24 stage 3 and 4 injuries out of 36 extravasation injuries with hyaluronidase infiltration and saline irrigation. None of the 36 cases required surgical debridement (Chowdhury 2004), suggesting good outcomes of the intervention, even at advanced stages of extravasation injury.

A case series highlighting drug-related extravasation injuries and intervention variations with saline and hyaluronidase also reported good outcomes. Physicians identified extravasation injury secondary to leakage of dopamine (n = 9), caffeine (n = 2), calcium (n = 2), and beta blocker (n = 1) in 14 neonates, 12 of whom were treated with hyaluronidase infiltration and aspiration, one with saline irrigation followed by aspiration, and another with hyaluronidase infiltration alone. Three patients developed skin necrosis, but all cases healed spontaneously (Casanova 2001). Clinicians have reported complete wound healing following extensive subcutaneous extravasation caused by use of corrosive drugs at cardiac catheterisation. Injury was managed with infiltration of hyaluronidase followed by liposuction and saline irrigation (Martin 1994).

Clinicians reported good outcomes in two preterm neonates at less than 29 weeks' gestation with total parenteral nutrition (TPN) fluid extravasation and treated with hyaluronidase infiltration and saline irrigation. Both lesions healed with minimal or no scarring (Davies 1994).

Two separate case reports described rapid tissue healing within three to five days in neonates with TPN fluid extravasation. Both individuals were treated with saline irrigation with prior hyaluronidase infiltration, but injury-irrigation intervals were different (90 minutes vs 4 hours) (Chen Y Y 1996; Siu 2007).

A retrospective review over three years at a regional neonatal unit described 56 confirmed cases of extravasation injury secondary to leakage of infusate of TPN, inotropic agents, calcium, potassium, sodium bicarbonate, and high-concentration dextrose. All injuries were irrigated with 500 mL of normal saline. Healthcare providers reported no episode of skin loss, and none of these neonates required reconstructive surgery (Harris 2001).

In a retrospective review of outcomes of extravasation injury following referral to a tertiary plastic surgical unit, review authors divided patients into two groups - 'early', that is, outcomes within the first 24 hours of extravasation; and 'late', that is, outcomes 24 hours after injury. Of 96 patients referred (ranging from premature infants to 70-year-olds), 44 were in the 'early' group and 52 in the 'late' group. A range of interventions were offered to the 'early' group, including saline flush-out (n = 37), saline flush-out and liposuction (n = 6), and liposuction alone (n = 1). The 'late'

group was offered conservative wound management only. Of 52 patients referred late, 8 (15%) healed without tissue necrosis, 17 (33%) showed only minor sloughing of the skin, and 27 (52%) had extensive damage to the soft tissue. Practitioners noted several complications including three amputations among babies in this 'late' group. The 'early' group, for whom saline irrigation was used, showed no signs of soft tissue damage in 39 (88.5%) cases and minor skin blistering with delayed healing in only five cases (11.5%). The range of agents causing extravasation was similar in the two groups (Gault 1993). This report describes only serious extravasation injuries referred to a tertiary plastic surgery centre, which may not be representative of all such injuries.

A recent case report describes infiltration with 'recombinant human hyaluronidase' (rHuPH20) without saline irrigation for the management of antibiotic extravasation injury for a term neonate (Kuensting 2010). The appearance of the swollen and tense foot returned to normal within 24 hours.

A report of 34 neonates with stage 3 and 4 extravasation injuries meticulously monitored and treated within 30 minutes of injury with saline irrigation and occlusive paraffin dressing indicated that neonates responded well to treatment without the need for secondary surgical intervention or secondary skin coverage procedures (Kostogloudis 2015).

A survey of current practice in the management of extravasation injury among neonates in Australia and New Zealand revealed that 16 of 24 centres followed written policy/standard practice in using saline wash-out via small incisions (Restieaux 2013).

We found no reports that advocated complete non-intervention (masterly inactivity) for the management of severe skin extravasation injury in neonates.

Extravasation injury is an inevitable complication of neonatal intensive care. Increasingly, babies born at the borderline of viability are being successfully treated in intensive care. Such babies require prolonged periods of intravenous access, including the need for vasoactive medications, TPN, and other infusions. Adequate training of medical and nursing staff in the care of central and peripheral lines, including frequent monitoring of the infusion site, has been advocated extensively in the literature as the most effective way of preventing extravasation injury (Brown 1979; Irving 2001; McCullen 2006; Tong 2007). Our review shows that many different methods are used in the management of extravasation injury for the neonate, including saline irrigation with or without prior hyaluronidase infiltration. All methods are reported to be successful without significant adverse events. Evidene suggests that mild extravasation injuries (stage 1 and stage 2) heal well with conservative management, but invasive methods are frequently required for more severe injuries (stage 3 and stage 4).

Given the limitations of the evidence at present, it seems prudent to use the saline irrigation technique for advanced stages of extravasation injury, especially stage 3 and 4 injury.

Summary of main results

We identified no randomised controlled trials evaluating whether saline irrigation or saline irrigation with prior hyaluronidase improves tissue healing in neonates with extravasation injury when compared with no intervention or normal wound care. We found 10 case reports or case series relevant to the question. Pooled data from these 10 case reports show that 234 out of 237 neonates who underwent saline irrigation with or without hyaluronidase infiltration exhibited complete wound healing without functional or cosmetic complications.

Overall completeness and applicability of evidence

Evidence provided in this review was obtained neither from randomised controlled trials (RCTs) nor from quasi-RCTs. No ongoing trials are registered at clinicaltrials.gov; the World Health Organization International Clinical Trials Registry Platform (www.whoint/ictrp/search/en/); or the ISRCTN Registry (www.isrctn.com). Saline irrigation for management of extravasation injuries in neonates cannot be advocated as standard treatment.

Quality of the evidence

We found no evidence from RCTs to support or refute the efficacy of saline irrigation or saline irrigation with prior hyaluronidase for improving tissue healing among neonates with extravasation injury when compared with no intervention or normal wound care. The quality of evidence derived for this review only from case series and case reports is 'very low', and true effects could be substantially different from those reported.

Potential biases in the review process

This was not applicable.

AUTHORS' CONCLUSIONS

Implications for practice

To date, no randomised controlled trials have investigated the effects of saline irrigation with or without prior hyaluronidase infiltration in the management of extravasation injuries among neonates. Saline irrigation for management of skin extravasation injuries, especially stage 3 and 4 injuries, has been shown to result in consistently better outcomes. However, on the basis of currently available evidence, we are unable to recommend "saline irrigation with or without prior infiltration with hyaluronidase infiltration in the management of extravasation injury in neonates" as standard practice.

Implications for research

Research should first be directed towards evaluating the efficacy and safety of this intervention through multi-centre randomised controlled trials. It will be important for investigators to determine effect size according to the timing of the intervention, the nature of the infusate, and severity of the injury at the time of intervention. In clinical science, if a randomised controlled trial cannot be conducted in the near future owing to variability and complexity of the clinical condition, a well-designed cohort study on a particular intervention method at a particular stage of extravasation injury will pave the way for developing a standard practice and achieving good outcomes for neonates everywhere.

ACKNOWLEDGEMENTS

Ms Diane Haughton (former Review Group Co-ordinator, Cochrane Neonatal).

Dr R Soll (Co-ordinating Editor, Cochrane Neonatal).

Dr J Sinclair.

Dr J Horbar.

Prof M Bracken.

Dr G Suresh.

Dr A Ohisson.

Ms Eryl Smith (Library Services - Glan Clwyd Hospital, UK).

Ms Susan Prosser (Library Services - Singleton Hospital, UK).

Ms Yolanda Montagne (Trial Search Co-ordinator, Cochrane Neonatal).

Ms Jennifer Spano (Cochrane Neonatal).

Ms Colleen Ovelman (Managing Editor, Cochrane Neonatal).

REFERENCES

References to studies excluded from this review

Casanova 2001 *{published data only}*

Casanova D, Bardot J, Magalon G. Emergency treatment of accidental infusion leakage in the newborn:report of 14 cases. *British Journal of Plastic Surgery* 2001;**54**(5):396-9.

Chen Y Y 1996 *{published data only}*

Chen YY, Wang HZ, Pan CH, Hsieh KS. Treatment of extravasation of intravenous fluid: a case report. *Clinical Neonatology* 1996;**3**:27-9.

Chowdhury 2004 *{published data only}*

Chowdhury M, Wong LH, Horn V, Eaton S, Pierro A. Extravasation injury in surgical neonates and children. *Proceedings of the Nutrition Society* 2004;**63 Suppl**(1):23A.

Davies 1994 *{published data only}*

Davies J, Gault D, Buchdahl R. Preventing the scars of neonatal intensive care. *Archives of Disease in Childhood* 1994;**70**(1):F50-1.

Gault 1993 *{published data only}*

Gault DT. Extravasation injuries. *British Journal of Plastic Surgery* 1993;**46**(2):91-6.

Harris 2001 *{published data only}*

Harris PA, Bradley S, Moss ALH. Limiting the damage of iatrogenic extravasation injury in neonates. *Plastic and Reconstructive Surgery* 2001;**107**(3):893-4.

Kostogloudis 2015 *{published data only}*

Kostogloudis N, Demiri E, Tsimponis A, Dionyssiou D, Ioannidis S, Chatziioannidis H, Nikolaidis N. Severe extravasation injuries in neonates: a report of 34 cases. *Pediatric Dermatology* 2015;**32**(6):830-5.

Kuensting 2010 *{published data only}*

Kuensting LL. Treatment of intravenous infiltrations in a neonate. *Journal of Pediatric Health Care* 2010;**24**(3):184-8.

Martin 1994 *{published data only}*

Martin PH, Carver N, Petros AJ. Use of liposuction and saline washout for the treatment of extensive subcutaneous extravasation of corrosive drugs. *British Journal of Anaesthesia* 1994;**72**(6):702-4.

Siu 2007 *{published data only}*

Siu SLY, Kwong KL, Poon SST, So KT. The use of hyaluronidase for treatment of extravasations in a premature infant. *HK Journal Paediatrics* 2007;**12**:130-2.

Additional references

Brown 1979

Brown AS, Hoelzer GJ, Piercy SA. Skin necrosis from extravasation of intravenous fluids in children. *Plastic and Reconstructive Surgery* 1979;**64**(2):145-50.

Bruera 1999

Bruera E, Neumann CM, Pituskin E, Calder K, Hanson J. A randomised controlled trial of local injections of hyaluronidase versus placebo in cancer patients receiving subcutaneous hydration. *Annals of Oncology* 1999;**10**(10):1255-8.

Cartlidge 1990

Cartlidge PH, Fox PE, Rutter N. The scars of newborn intensive care. *Early Human Development* 1990;**2**(1):1-10.

Chandanvasu 1986

Chandanvasu O, Garrow E, Valda V, Alsheikh S, Vega SD. A new method for the prevention of skin sloughs and necrosis secondary to intravenous infiltration. *American Journal of Perinatology* 1986;**3**(1):4-5.

Cho 2007

CHo KY, Lee SJ, Burm JS, Park EA. Successful combined treatment of accidental infusion leakage in the newborn: report of 14 cases. *British Journal of Plastic Surgery* 2001;**54**(5):396-9.

Davidson 1985

Davidson DC, Gilbert J. Severe extravasation injury. *British Medical Journal* 1985;**291**(6489):217.

Falcone 1989

Falcone PA, Barrell DT, Jeyarajah DR, Grossman JAI. Nonoperative management of full-thickness intravenous extravasation injuries in premature neonates using enzymatic debridement. *Annals of Plastic Surgery* 1989;**22**(2):146-9.

Flemmer 1993

Flemmer L, Chan JS. A paediatric protocol for management of extravasation injuries. *Pediatric Nursing* 1993;**19**(4):355-8.

Fox 1998

Fox PE, Rutter N. The childhood scars of newborn intensive care. *Early Human Development* 1998;**51**(2):171-7.

Friedman 1998

Friedman J. Plastic surgical problems in the neonatal intensive care unit. *Clinics in Plastic Surgery* 1998;**25**(4):599-617.

Fullilove 1997

Fullilove S, Fixsen J. Major limb deformities as complications of vascular access in neonates. *Paediatric Anesthesia* 1997;**7**(3):247-50.

Goutos 2014

Goutos I, Cogswell L.K, Giele H. Extravasation Injuries: a review. *The Journal of Hand Surgery (European Volume)* 2014;**39E**(8):808-818.

GRADEpro GDT [Computer program]

Grade Working Group, McMaster University. GRADEpro [www.gradepro.org]. Version 14 September 2014. Hamilton (ON): Grade Working Group, McMaster University, 2014.

Hadaway 2007

Hadaway L. Infiltration and extravasation. *American Journal of Nursing* 2007;**107**(8):64-72.

Higgins 2011

Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Irving 1999

Irving V. Management of a neonatal wound on a newborn infant. *Journal of Wound Care* 1999;**8**(10):485-6.

Irving 2001

Irving V. Managing extravasation injuries in preterm neonates. *Nursing Times* 2001;**97**(35):40-4.

Jaworski 1950

Jaworski A, Farley JE Jr. Hyaluronidase in administration of fluids. *American Journal of Diseases of Children* 1950;**79**(1):59-64.

Kumar 2001

Kumar RJ, Pegg SP, Kimble RM. Management of extravasation injuries. *ANZ Journal of Surgery* 2001;**71**:285-9.

Lee 2013

Lee HJ, Kwon SH, Choi JW, Park KC, Youn SW, Huh CH, et al. The management of infantile extravasation injury using maternal platelet-rich plasma. *Pediatric Dermatology* 2013;**30**(6):e114-7.

McCullen 2006

McCullen KL, Pieper B. A retrospective chart review of risk factors for extravasation among neonates receiving peripheral intravascular fluids. *Journal of Wound, Ostomy and Continence Nursing* 2006;**33**(2):133-9.

Millam 1988

Millam DA. Managing complications of I.V. therapy. *Nursing* 1988;**18**:34-43.

Moss 2001

Moss ALH, Turner M, Rose V, Harris PA. Management of extravasation injury. British Association of Plastic Surgeons Summer Meeting. July 2001.

Onesti 2012

Onesti MG, Carella S, Maruccia M, Ciotti M, Scuderi N. The use of Hyalomatrix PA in the treatment of extravasation affecting premature neonates. *Plastic and Reconstructive Surgery* 2012;**129**(1):219e-21e.

Patnaik 2004

Patnaik SK, Patnaik SK. Necrosis in extravasation incidents is a tip of the iceberg. [Letter]. *Archives of Disease in Childhood. Fetal and Neonatal Edition* 2004;**89**(3):www.fn.bmj.com/cgi/eletters/89/3/F274-5.

PPAG 2005

Pediatric Pharmacy Advocacy Group, Inc. Position statement on hyaluronidase injection. Child Advocacy, Pediatric Pharmacy 2005.

Ramasethu 2004

Ramasethu J. Pharmacology review: prevention and management of extravasation injuries in neonates. *Neoreviews* 2004;**5**(11):e491-6.

Restieaux 2013

Restieaux M, Maw A, Broadbent R, Jackson P, Barker D, Wheeler B. Neonatal extravasation injury: prevention and management in Australia and New Zealand - a survey of current practice. *BMC Pediatrics* 11 March 2013;**13:34**:doi:10.1186/1471-2431 - 13-34. [BioMed Central]

Reynolds 2007

Reynolds BC. Neonatal extravasation injury: case report. *Infant* 2007;**3**(6):230-2.

Reynolds 2014

Reynolds PM, MacLaren R, Mueller SW, Fish DN, Kiser TH. Management of extravasation injuries: a focused evaluation of noncytotoxic medications. *Pharmacotherapy* 2014;**34**(6):617-32.

Sawatzky-Dickson 2006

Sawatzky-Dickson D, Bodnaryk K. Neonatal intravenous extravasation injuries: evaluation of a wound care protocol. *Neonatal Network* 2006;**25**(1):13-9.

Schünemann 2013

Schünemann H, Brożek J, Guyatt G, Oxman A, editors. GRADE Working Group. GRADE Handbook for Grading Quality of Evidence and Strength of Recommendations. https://gdt.gradepro.org/app/handbook/handbook.html [Updated October 2013].

Thomas 1997

Thomas S, Rowe HN, Keats J, Morgan RJH. The management of extravasation injury in neonates. World Wide Wounds 1997, issue Edition 1.

Tong 2007

Tong R. Preventing extravasation injuries in neonates. *Paediatric Nursing* 2007;**19**(8):22-5.

Valente 2001

Valente JH, Forti RJ, Freundlich LF, Zandieh SO, Crain EF. Wound irrigation: tap water or saline. Proceedings of the Pediatric Academic Society Meeting, Abstract 430. 2001.

Wilkins 2004

Wilkins CE, Emmerson AJ. Extravasation injuries on regional neonatal units. *Archives of Disease in Childhood. Fetal and Neonatal Edition* 2004;**89**(3):F274-5.

CHARACTERISTICS OF STUDIES

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Casanova 2001	Case series
Chen Y Y 1996	Case report
Chowdhury 2004	Retrospective review of 31 cases
Davies 1994	Case report
Gault 1993	Retrospective review of 96 cases
Harris 2001	Retrospective review
Kostogloudis 2015	Case report
Kuensting 2010	Case report
Martin 1994	Case report
Siu 2007	Case report

All 10 studies are either case reports or case series. Time to intervention from extravasation is highly variable. In all 10 studies, participants were neonates only. All 10 studies reported their outcomes as complete wound healing and no functional and cosmetic disability.

ADDITIONAL TABLES

Table 1. Summary of excluded studies - study design, population, intervention, and outcome

Study	Type of study	Number of neonates	Extravasation	Intervention	Outcome
Casanova 2001	Case series	14 neonates	Dopamine - 9 Caffeine - 2 Calcium - 2 Beta blocker - 1	Hyaluronidase infiltration and aspiration - 12 Saline irrigation and aspiration - 1 Hyaluronidase infiltration alone - 1	3 cases developed skin necrosis but healed spontaneously
Chen Y Y 1996	Case report	1 neonate	Total parenteral nutrition (TPN)	Infiltration with hyaluronidase with saline irrigation	Healing in 3 days
Chowdhury 2004	Retrospective review of 31 cases	31 neonates had 36 extravasations	TPN - 13 Medications - 10 Blood products - 6 Crystalloids - 5	Hyaluronidase infiltration and saline irrigation used for 24 extravasation injuries	No surgical graft required

Table 1. Summary of excluded studies - study design, population, intervention, and outcome *(Continued)*

			Contrast - 2		
Davies 1994	Case report	2 preterm neonate less than 29 weeks gestation	TPN	Hyaluronidase infiltration and saline irrigation	Minimal or no scarring, no functional sequelae
Gault 1993	Retrospective review of 96 cases	Total 96 cases referred to a tertiary plastic surgical unit (age range - preterm neonate to 72 years - exact distribution not mentioned) 44 early referrals, i.e. within 24 hours 52 late referral, i.e. after 24 hours	TPN Inotrope Ca KCl Bicarbonate Dextrose: 10%-20% Chemotherapeutics Contrast Antibiotics *(exact numbers not mentioned)*	Early referral group: 44 (saline irrigation alone - 37, liposuction and saline irrigation - 6, liposuction alone - 1) Late referral group: wound and surgical management	Early referral group: 39 (88.5%) no soft tissue damage, 5 (11.5%) minor skin blistering Late referral group: 8 (15%) healed without tissue necrosis, 17 (33%) minor skin sloughing, 27 (52%) extensive damage to tissues - 3 amputations
Harris 2001	Retrospective review	56 neonates	TPN Inotrope Calcium Potassium chloride Sodium bicarbonate High concentration of dextrose *(exact numbers not mentioned)*	Saline irrigation alone	No skin loss. None required reconstructive surgery
Kostogloudis 2015	Case report	34 neonates	TPN - 28 10% dextrose - 4 Second-generation cephalosporin - 2	Saline irrigation followed by topical application of paraffin-impregnated gauze and povidone-iodine-soaked gauze dressing	In 21 infants, no signs of soft tissue damage by 24 hours of treatment Minor findings still present for a few days in 7 patents after treatment Ischaemic signs present in 6 patients subsided within 25 days
Kuensting 2010	Case report	1 neonate	Antibiotics	Infiltration with recombinant human hyaluronidase (rHuPH20)	Wound healed completely by 8 days

Table 1. Summary of excluded studies - study design, population, intervention, and outcome *(Continued)*

Martin 1994	Case report	1 neonate	Dobutamine, adrenaline, 8.4% sodium bicarbonate, 10% calcium gluconate	Infiltration of hyaluronidase followed by liposuction and saline irrigation	No signs of soft tissue damage at 2 weeks
Siu 2007	Case report	1 neonate	TPN	Hyaluronidase infiltration and saline irrigation	Healed fully by 5 days

Table 2. Summary of excluded studies - stage of extravasation and intervention and its outcome

Study	Stage of extravasation	Intervention	Outcome	Reason for exclusion
Casanova 2001	Skin necrosis (stage 3): n = 3 Swelling, oedema, discolouration (stage 1-2): n = 11	Hyaluronidase and aspiration - 12 cases Hyaluronidase infiltration alone - 1 Saline irrigation and aspiration - 1 Treatment allocation not specified by stage of injury	No sequelae	Neither a randomised nor a quasi-randomised study
Chen Y Y 1996	Swelling, erythema, and induration (stage 3): n = 1	Hyaluronidase and saline irrigation	No sequelae	Neither a randomised nor a quasi-randomised study
Chowdhury 2004	Erythema and oedema (stage 1-2): n = 12 Skin necrosis (stage 3): n = 24	Stage 1-2 - standard wound management Stage 3 - hyaluronidase and saline irrigation	No sequelae No sequelae	Neither a randomised nor a quasi-randomised study
Davies 1994	Skin necrosis (stage 3): n = 2	Hyaluronidase and saline irrigation	Minimal scarring, no sequelae	Neither a randomised nor a quasi-randomised study
Gault 1993	Skin necrosis (stage 3): Early referral: n = 44 Delayed referral (stage 3-4): n = 52	Stage 3: Saline irrigation alone: n = 37 Liposuction and saline irrigation: n = 6 Liposuction alone: n = 1 Stage 3-4: Wound debridement and surgical flap	No sequelae 8 (15%) healed without tissue necrosis, 17 (33%) minor skin sloughing, 27 (52%) extensive damage to tissues - 3 amputations	Neither a randomised nor a quasi-randomised study
Harris 2001	Exact stage of extravasation injury not specified: n = 56	Saline irrigation	No sequelae	Neither a randomised nor a quasi-randomised study
Kostogloudis 2015	Stage 3 and stage 4 extravasation	Saline irrigation within 30 minutes of extravasation injury	None of the wounds needed secondary skin	Neither a randomised nor a quasi-randomised study

Table 2. Summary of excluded studies - stage of extravasation and intervention and its outcome *(Continued)*

			coverage procedures	
Kuensting 2010	Discolouration, oedema, cool, pulses not palpable (stage 4): n = 1	Infiltration with recombinant human hyaluronidase (rHuPH20)	No sequelae	Neither a randomised nor a quasi-randomised study
Martin 1994	Oedema, pallor, cold, and no capillary filling	Infiltration with hyaluronidase, liposuction, and saline irrigation	No sequelae	Neither a randomised nor a quasi-randomised study
Siu 2007	Skin necrosis (stage 3): n = 1	Hyaluronidase and saline irrigation	No sequelae	Neither a randomised nor a quasi-randomised study

APPENDICES

Appendix 1. Search methods for 2017 update

PubMed: ((infant, newborn[MeSH] OR newborn OR neonate OR neonatal OR premature OR low birth weight OR VLBW OR LBW or infan* or neonat*) AND (randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab]) NOT (animals [mh] NOT humans [mh]))

Embase: (infant, newborn or newborn or neonate or neonatal or premature or very low birth weight or low birth weight or VLBW or LBW or Newborn or infan* or neonat*) AND (human not animal) AND (randomized controlled trial or controlled clinical trial or randomized or placebo or clinical trials as topic or randomly or trial or clinical trial)

CINAHL: (infant, newborn OR newborn OR neonate OR neonatal OR premature OR low birth weight OR VLBW OR LBW or Newborn or infan* or neonat*) AND (randomized controlled trial OR controlled clinical trial OR randomized OR placebo OR clinical trials as topic OR randomly OR trial OR PT clinical trial)

Cochrane Library: (infant or newborn or neonate or neonatal or premature or preterm or very low birth weight or low birth weight or VLBW or LBW)

Google Scholar: Reverse citaion on relavant articles

Appendix 2. Search methods for 2012 review

MeSH subject headings were infant, newborn, neonates, preterm infant, extravasation, saline, hyaluronidase, irrigation, therapeutic irrigation, and infiltration.

Summary of literature search details

MEDLINE- (searched from 1950 - 24/06/2011) 28 references retrieved.

Embase- (searched from 1980 - 24/06/2011) 26 references retrieved.

CINAHL- (searched from 1981 - 28/06/2011) 38 references retrieved.

Cochrane Central Database of Clinical Trials (CENTRAL) - (searched up to 28/06/2011) 26 references retrieved.

Web of Science- (searched from 1911 - 11/07/2011) 1 reference retrieved.

***Total references retrieved (after de-duplication):* 64**

MEDLINE (Ovid) - full search up to 24 June 2011

1 "Extravasation of Diagnostic and Therapeutic Materials"/pc, su, th (Prevention & Control, Surgery, Therapy)

2 Saline Solution, Hypertonic/or Saline.mp.

3 1 and 2

4 limit 3 to (English language and "newborn infant (birth to 1 month)")

5 "Extravasation of diagnostic and Therapeutic Materials"/

6 2 and 5

7 limit 6 to (English language and "newborn infant (birth to 1 month)")

8 from 4 keep 1-3

9 extravasation.mp. or inflammation/

10 swelling.mp. or Edema/

11 Erythema/

12 9 or 10 or 11

13 catheterization, Peripheral/ or Infusions, Intravenous/

14 2 and 12 and 13

15 limit 14 to (English language and "newborn infant (birth to 1 month)")

16 neonate.mp

17 Infant, Newborn/or Infant, Premature/

18 16 or 17

19 14 and 18

20 3 and 18

21 13 and 18

22 2 and 21

23 5 and 18

24 limit 23 to English language

25 limit 24 to yr=Current

26 Therapeutic irrigation/ or irrigation.mp

27 hyaluronidase.mp. (mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier)

28 5 and 26 and 27

29 5 and 27

30 18 and 29

Embase (Ovid) - up to 27 June 2011

1 "Extravasation of Diagnostic and Therapeutic materials"/

2 extravasation.mp.

3 1 or 2

4 Infusions, Intravenous/

5 Catheterization, Peripheral/

6 4 or 5

7 Inflammation/

8 Erythema/

9 swelling.mp.

10 Edema/

11 7 or 8 or 9 or 10

12 6 and 11

13 3 or 12

14 Saline Solution, Hypertonic/ or Saline.mp.

15 hyaluronidase.mp. or hyaluronoglucosaminidase/

16 Therapeutic irrigation/ or Irrigation.mp.

17 13 and 14 and 15 and 16

18 13 and 14 and 15

19 limit 18 to English language (not limited to age)

20 limit 19 to "newborn infant (birth to 1 month)"(limit not valid in Embase; records were retained)

21 13 and 14 and 16

22 limit 21 to English language

23 13 and 14

24 limit 23 to English language

25 limit 20 to infant

26 2newborn"/

27 infant/

28 neonatal.mp.

29 neonate.mp.(mp=title,abstract,subject heading, heading word, drug trade name, original title, device manufacturer, drug manufacturer,device trade name, keyword)

30 26 or 27 or 28 or 29

24 and 30

Web of Science - up to 11/07/2011

#1 Topic = (extravasation)

#2 Title = Extravasation

#3 #1 AND #2

#4 Topic = Saline

#5 Topic = hyaluronidase

#6 Topic = therapeutic irrigation

#8 #7 or #6

#9 #8 AND #5 AND #4 AND #3

#10 #5 AND #4 AND #3

#11 #8 AND #4 AND #3

#12 #4 AND #3

#13 #4 AND #3 limited to2007 - 2010

#14 #4 AND #3 limited to 2007 - 2010 and Neonat #10

#15 #4 AND #3 limited to 2011

CINAHL (EBSCO) - up to 28 June 2011

S21 S3 or S11

Limiters - English language; published date from 20000101-20111231; age groups: infant, newborn: birth, 1 month, infant 1-23 months

Expanders - also search within the full text of articles

Search modes - Boolean/phrase

S20 S3 or S11

Limiters - English language; age groups: infant, newborn: birth, 1 month, infant 1-23 months

Expanders - also search within the full text of articles

Search modes - Boolean/phrase

S19 S12 and S13

Limiters - age groups: infant, newborn: birth, 1 month, infant 1-23 months

Expanders - also search within the full text of articles

Search modes - Boolean/phrase

S18 S12 and S13

Expanders - also search within the full text of articles

Search modes - Boolean/phrase

S17 S12 and S13 and S14

Expanders - also search within the full text of articles

Search modes - Boolean/phrase

S16 S12 and S13 and S14 and S15

Expanders - also search within the full text of articles

Search modes - Boolean/phrase

S15 (MH " Feeding Tube irrigation") OR (MH " Catheter irrigation, Vascular") OR (MH " Irrigation")

Expanders - also search within the full text of articles

Search modes - Boolean/phrase

S14 (MH " HYaluronidase")

Expanders - also search within the full text of articles

Search modes - Boolean/phrase

S13 (MH "Saline Solution, Hypertonic") OR " Saline"

Expanders - also search within the full text of articles

Search modes - Boolean/phrase

S12 S3 or S11

Expanders - also search within the full text of articles

Search modes - Boolean/phrase

S11 S6 and S10

Expanders - also search within the full text of articles

Search modes - Boolean/phrase

S10 S7 or S8 or S9

Expanders - also search within the full text of articles

Search modes - Boolean/phrase

S9 (MH " Erythema")

Expanders - also search within the full text of articles

Search modes - Boolean/phrase

S8 (MH "inflammation") OR "Inflammation"

Expanders - also search within the full text of articles

Search modes - Boolean/phrase

S7 "swelling" OR (MH "Edema")

Expanders - also search within the full text of articles

Search modes - Boolean/phrase

S6 S4 OR S5

Expanders - also search within the full text of articles

Search modes - Boolean/phrase

S5 (MH " Catheterization, Peripheral") OR (MH " Catheterization, Peripheral Central venous")

Expanders - also search within the full text of articles

Search modes - Boolean/phrase

S4 (MH "intravenous therapy") OR (MH " Fluid Resuscitation")

Expanders - also search within the full text of articles

Search modes - Boolean/phrase

S3 S1 or S2

Expanders - also search within the full text of articles

Search modes - Boolean/phrase

S2 "extravasation"

Expanders - also search within the full text of articles

Search modes - Boolean/phrase

S1 (MH "Extravasation of Diagnostic and Therapeutic Materials")

Expanders - also search within the full text of articles

Search modes - Boolean/phrase

The Cochrane Central Register of Controlled trials (CENTRAL) (2011, Issue 2) in the Cochrane Library - 28 June 2011

#1 MeSH descriptor **Extravasation of Diagnostic and Therapeutic Materials** explode all trees

#2 extravasation

#3 (#1 OR #2)

#4 MeSH descriptor **Infusions, Intravenous** explode all trees

#5 MeSH descriptor **Catheterization, Peripheral** explode all trees

#6 (#4 OR #5)

#7 MeSH descriptor **inflammation**, this term only

#8 MeSH descriptor**Erythema** explode all trees

#9 swelling

#10 edema

#11 (#7 OR #8 OR #9 OR10)

#12 (#6 AND #11)

#13 (#3 OR #12)

#14 MeSH descriptor **Saline Solution, hypertonic** explode all trees

#15 saline

#17 hyaluronidase

#18 MeSH descriptor **Hyaluronoglucosaminidase** explode all trees

#19 (#17 OR #18)

#20 MeSH descriptor **Therapeutic Irrigation**, this term only

#21 irrigation

#22 (#20 OR #21)

#23 (**#13** AND **#16** AND **#19** AND **#22**)

#24 (#13 AND #16 AND #19)

#25 (#13 AND #16)

#26 (#13 AND #16)

#27 neonat*

#28 MeSH descriptor **Infant, Newborn** explode all trees

#29 infant

#30 (#27 Or #28 Or #29)

#31 (#25 AND #30)

#32 (#13 AND #30)

#33 (#32 AND NOT #25)

#34 (#33 AND NOT #31)

Appendix 3. Risk of bias tool

We used the standard methods of the Cochrane Collaboration and the Cochrane Neonatal Review Group to assess the methodological quality (to meet the validity criteria) of trials. For each trial, we sought information regarding the method of randomisation and blinding and reporting of all outcomes for all infants enrolled in the trial. We assessed each criterion as low, high, or unclear risk. Two review authors separately assessed each study. We resolved disagreements by discussion. We added this information to the Characteristics of included studies table. We evaluated the following issues and entered the findings into the risk of bias table.

1. Sequence generation (checking for possible selection bias). Was the allocation sequence adequately generated?

For each included study, we categorised the method used to generate the allocation sequence as:

a. Low risk (any truly random process, e.g. random number table; computer random number generator);

b. High risk (any non-random process, e.g. odd or even date of birth; hospital or clinic record number); or

c. Unclear risk.

2. Allocation concealment (checking for possible selection bias). Was allocation adequately concealed?

For each included study, we categorised the method used to conceal the allocation sequence as:

a. Low risk (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);

b. High risk (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth); or

c. Unclear risk.

3. Blinding of participants and personnel (checking for possible performance bias). Was knowledge of the allocated intervention adequately prevented during the study?

For each included study, we categorised the methods used to blind study participants and personnel from knowledge of which intervention a participant received. Blinding was assessed separately for different outcomes or classes of outcomes. We categorised the methods as:

a. Low risk, high risk, or unclear risk for participants; and

b. Low risk, high risk, or unclear risk for personnel.

4. Blinding of outcome assessment (checking for possible detection bias). Was knowledge of the allocated intervention adequately prevented at the time of outcome assessment?

For each included study, we categorised the methods used to blind outcome assessment. Blinding was assessed separately for different outcomes or classes of outcomes. We categorised the methods as:

a. Low risk for outcome assessors;

b. High risk for outcome assessors; or

c. Unclear risk for outcome assessors.

5. Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations). Were incomplete outcome data adequately addressed?

For each included study and for each outcome, we described completeness of data including attrition and exclusions from the analysis. We noted whether attrition and exclusions were reported, the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion when reported, and whether missing data were balanced across groups or were related to outcomes. When sufficient information was reported or supplied by trial authors, we re-included missing data in the analyses. We categorised the methods as:

a. Low risk (< 20% missing data);

b. High risk (≥ 20% missing data); or

c. Unclear risk.

6. Selective reporting bias. Are reports of the study free of the suggestion of selective outcome reporting?

For each included study, we described how we investigated the possibility of selective outcome reporting bias and what we found. We assessed the methods as:

a. Low risk (when it is clear that all of the study's prespecified outcomes and all expected outcomes of interest to the review have been reported);

b. High risk (when not all of the study's prespecified outcomes have been reported; when one or more reported primary outcomes were not prespecified outcomes of interest and are reported incompletely and so cannot be used; when study fails to include results of a key outcome that would have been expected to have been reported); or

c. Unclear risk.

7. Other sources of bias. Was the study apparently free of other problems that could put it at high risk of bias?

For each included study, we described any important concerns that we had about other possible sources of bias (e.g. whether a potential source of bias was related to the specific study design, whether the trial was stopped early owing to some data-dependent process). We assessed whether each study was free of other problems that could put it at risk of bias as:

a. Low risk;

b. High risk; or

c. Unclear risk.

If needed, we explored the impact of the level of bias by undertaking sensitivity analyses.

Appendix 4. Reason for increased duration of this update from the original review published in February 2012

A prospective surveillance on literature by the review authors yielded no relevant RCTs or quasi-RCTs and even cohort studies. Hence the review authors decided to defer updating this review until 2017.

Appendix 5. Next update of this review

The review authors propose to update this review with an enhanced duration of four years by 2021, with the hope that more relevant studies will be published in the literature by that time.

WHAT'S NEW

Date	Event	Description
17 May 2017	New citation required but conclusions have not changed	An updated literature search revealed no new studies for inclusion
4 March 2017	New search has been performed	Updated review using Cochrane search methods

CONTRIBUTIONS OF AUTHORS

S Banerjee conceptualised this review and was involved in all stages and guided preparation of this review.

N Goel contributed to the literature search, study selection, data management, communications, and development of the Discussion and Conclusions, and was involved in all stages of preparation of this review.

PN Gopalakrishnan contributed to the literature search, study selection, data management, communications, and development of the Discussion and Conclusions, and was involved in all stages of preparation of this review.

DECLARATIONS OF INTEREST

We have no interests to declare.

SOURCES OF SUPPORT

Internal sources

- Library Services, Singleton Hospital, ABM University NHS Trust, Swansea, UK.
- Department of Neonatology, Singleton Hospital, ABM University Health Board, Swansea, UK.
- Library Services, Glan Clwyd Hospital, UK.
- Library Services, NHS Lanarkshire, UK.

External sources

- Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Department of Health and Human Services, USA.

  Editorial support of the Cochrane Neonatal Review Group has been funded by Federal funds from the Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Department of Health and Human Services, USA, under Contract No. HHSN275201600005C

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We have no deviation from the original protocol to report.

INDEX TERMS

Medical Subject Headings (MeSH)

Extravasation of Diagnostic and Therapeutic Materials [*therapy]; Hyaluronoglucosaminidase [*therapeutic use]; Medical Records; Skin [*injuries]; Sodium Chloride [*therapeutic use]; Solutions; Therapeutic Irrigation [methods]

MeSH check words

Humans; Infant, Newborn